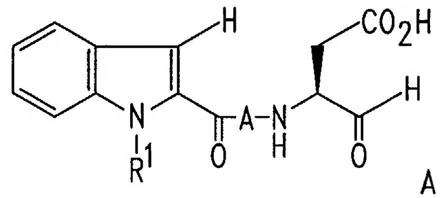
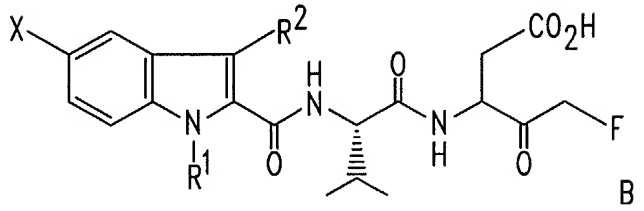


A

TABLE 1 50% INHIBITORY CONCENTRATIONS IC_{50} FOR FORMULA A				
Example	R^1	A	mICE $IC_{50}(\mu M)$	CPP32 $IC_{50}(\mu M)$
4	CH_3	Ala	0.177	>10
7	CH_3	Pro	11.7	>50
10	CH_3	Val	0.531	2.48
13	CH_3	Leu	5.52	5.62
16	CH_3	Phe	3.34	49.8
21	CH_3	Gly	34.7	>50
24	CH_2Ph	Ala	0.393	>50
27	$(CH_2)_2CH{=}CH_2$	Val	0.313	1.45
30	CH_2CO_2H	Ala	1.63	>50
33	$(CH_2)_2CO_2H$	Ala	0.198	>50
reference	--	--	0.064	47.0

Fig. 1



B

TABLE 2
DISSOCIATION CONSTANT Ki AND INACTIVATION RATE
k_3/Ki FOR FORMULA B

Example	R^1	R^2	X	mICE Ki (μM)	mICE k_3/Ki ($M^{-1}s^{-1}$)	CPP32 Ki (μM)	CPP32 k_3/Ki ($M^{-1}s^{-1}$)	Mch2 Ki (μM)	Mch2 k_3/Ki ($M^{-1}s^{-1}$)	Mch5 Ki (μM)	Mch5 k_3/Ki ($M^{-1}s^{-1}$)
43	CH_3	CH_3	H	1.40	2,860	0.960	13,400	0.017	58,800	0.062	21,500
46	CH_3	Cl	H	1.68	6,150	0.830	25,900	ND	ND	0.099	37,000
49	CH_3	Cl	F	1.10	7,120	0.493	72,700	0.014	71,400	0.054	52,500
52	$(CH_2)_3Ph$	H	H	0.133	45,100	0.742	33,700	0.024	41,700	0.077	32,500
55	Ph	H	H	0.843	8,900	0.110	74,200	0.036	55,600	0.043	35,300
58	CH_2CO_2H	H	H	0.327	16,800	0.125	58,700	0.051	19,600	0.038	127,000
61	CH_3	H	H	0.240	41,700	0.520	21,200	0.033	30,300	0.026	38,500
62	CH_3	CH_3	F	0.397	7,560	0.113	44,200	0.040	25,000	0.102	29,400
63	$(CH_2)_2CH=CH_2$	H	H	0.327	18,300	0.125	56,000	0.104	19,200	0.038	131,600
64	CH_3	H	F	0.234	21,400	0.180	38,900	0.052	38,500	0.063	47,600
65	CH_3	$CH_2CH(CH_3)_2$	H	4.56	1,540	2.28	7,910	0.023	43,500	0.063	31,700
66	CH_3	$(CH_2)_2Ph$	H	0.632	14,200	0.505	21,800	0.038	26,300	0.051	39,200
67	CH_3	H	OCH_2Ph	0.739	14,900	0.346	31,800	0.040	25,000	0.062	16,100
reference	--	--	--	0.015	278,000	0.820	14,600	0.594	3,370	0.018	83,300

Fig. 2

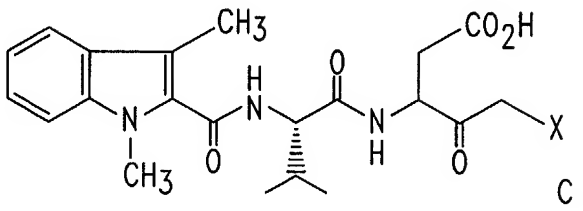
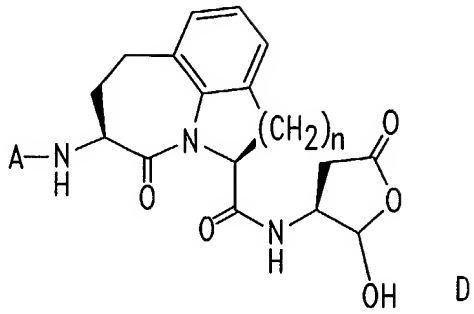


TABLE 3
DISSOCIATION CONSTANT Ki AND INACTIVATION RATE
k_3/Ki FOR FORMULA C

Example	X	mICE		CPP32		Mch2		Mch5	
		Ki (μM)	k_3/Ki ($M^{-1}s^{-1}$)	Ki (μM)	k_3/Ki ($M^{-1}s^{-1}$)	Ki (μM)	k_3/Ki ($M^{-1}s^{-1}$)	Ki (μM)	k_3/Ki ($M^{-1}s^{-1}$)
43	F	1.40	2,860	0.960	13,400	0.017	58,800	0.062	21,500
70	OCO (2, 6-di-Cl-C_6H_3)	1.16	3,460	0.052	57,700	0.030	33,300	0.364	2,750
71	OPO (C_6H_5)$_2$	0.124	24,200	0.046	65,200	0.060	50,000	0.022	45,500
72	O (1-Ph-3-CF_3-pyrazol-5-yl)	0.873	1,150	0.300	16,700	0.050	20,000	1.39	720
73	O 3-$CONH_2$-2-naphthyl)	8.00	250	1.58	0	0.632	1,580	0.213	0
74	O (2-$CONH_2$-1-phenyl)	0.297	3,370	0.419	4,770	0.340	2,940	0.547	0
75	OPO (CH_3)$_2$	4.33	1,850	1.05	7,660	ND	ND	0.663	1,510
reference	--	0.015	278,00	0.820	14,600	0.594	3,370	0.018	83,300

Fig. 3

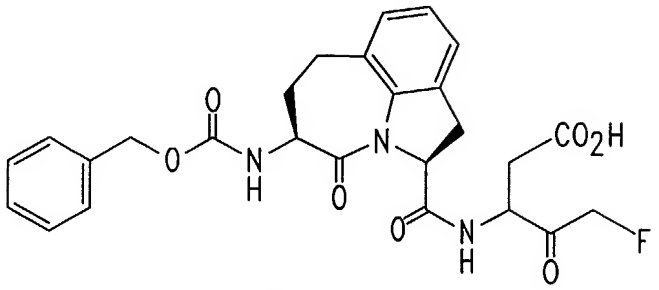


D

TABLE 4
50% INHIBITORY CONCENTRATIONS IC_{50}
FOR FORMULA D

Example No.	A	n	mICE $IC_{50}(\mu M)$	CPP32 $IC_{50}(\mu M)$	MCH-2 $IC_{50}(\mu M)$	MCH-3 $IC_{50}(\mu M)$	MCH-5 $IC_{50}(\mu M)$
78	Cbz	1	0.019	1.03	40.1	6.96	>10
82	Ac-Asp	1	0.694	0.0014	6.47	0.145	2.09
85	succinyl	1	0.571	0.245	1.81	2.83	7.98
88	Cbz-Asp	1	0.096	0.00052	ND	0.084	1.19
91	dihydrocinnamoyl	1	0.045	0.780	>10	32.6	18.7
94	Ac	1	3.07	3.87	>10	>50	>50
100	Benzoyl	1	0.159	8.77	>50	>50	4.63
97	1-Naphthoyl	1	0.010	2.91	>50	12.3	1.09
103	Cbz	2	0.026	0.437	32.0	1.11	2.06
reference	–	–	0.064	47.0	>10	>10	2.96

Fig. 4



Example 106

TABLE 5
DISSOCIATION CONSTANT Ki AND INACTIVATION RATE
k_3/Ki FOR EXAMPLE 106

	Example 106		Reference	
Enzyme	Ki (μM)	k_3/Ki ($M^{-1}s^{-1}$)	Ki (μM)	k_3/Ki ($M^{-1}s^{-1}$)
mICE	0.0005	12,000,000	0.015	214,000
CPP32	0.012	960,000	0.820	12,200
MCH-2	0.033	25,000	0.594	2,950
MCH-5	0.022	98,000	0.018	83,300

Fig. 5

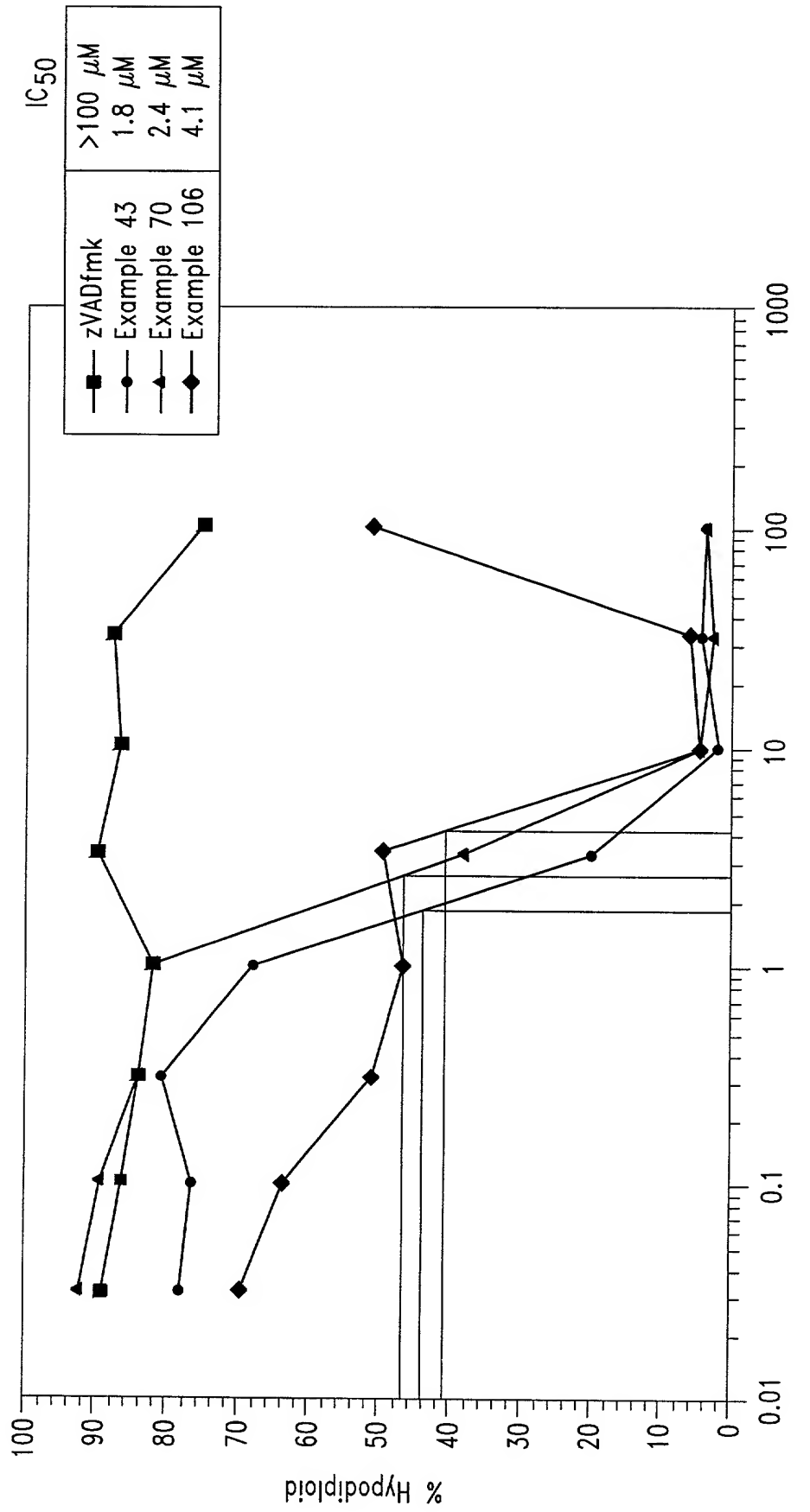

FACS Analysis of Propidium Iodide Labelled Neutrophils:
48 Hour Time Point
% Hypodiploid
Concentration (μM)
IC50
zVADfmk >100 μM
Example 43 1.8 μM
Example 70 2.4 μM
Example 106 4.1 μM
100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
1000

Fig. 6

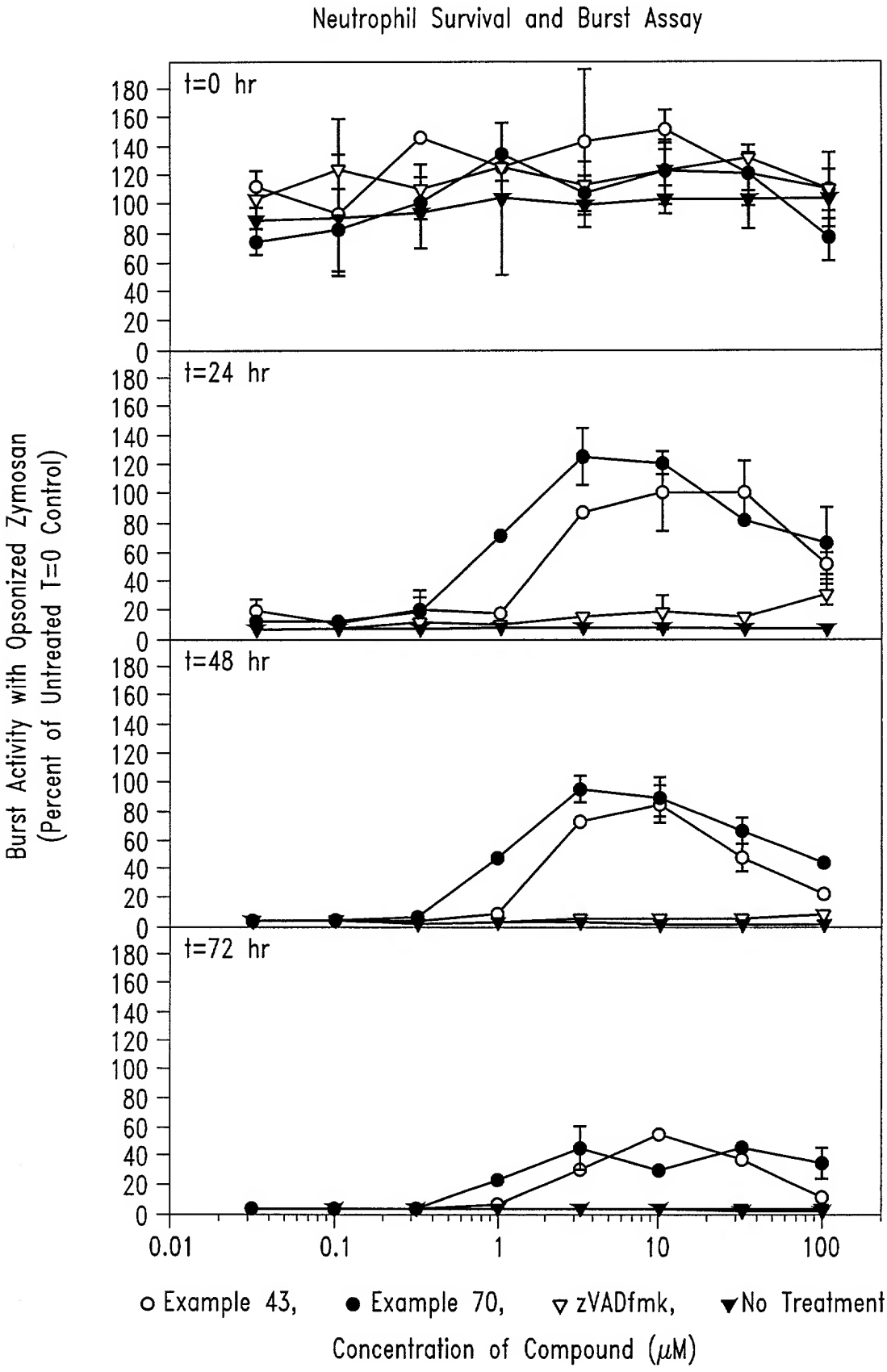

Neutrophil Survival and Burst Assay
t=0 hr
t=24 hr
t=48 hr
t=72 hr
Burst Activity with Opsonized Zymosan
(Percent of Untreated T=0 Control)
0
20
40
60
80
100
120
140
160
180
0.01
0.1
1
10
100
○ Example 43, ● Example 70, ▽ zVADfmk, ▼No Treatment
Concentration of Compound (μM)

Fig. 7